# Acute Heart Failure
## From The Emergency Department to the Intensive Care Unit

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**KEYWORDS**

• Acute heart failure • Cardiogenic shock • Guideline-directed medical therapy
• Emergency department • Intensive care unit

**KEY POINTS**

- Acute heart failure (AHF) is a leading cause of hospitalization and generates a significant economic burden worldwide.
- Diagnostic tools and management vary by clinical acuity and phase of care.
- Hospitalization is an opportunity to initiate evidence-based care in de novo heart failure and optimize therapy for those with acute decompensations.
- More research is needed to guide risk stratification and optimize linkage to outpatient care post-hospitalization.

### INTRODUCTION

Acute heart failure (AHF) is one of the most frequent reasons for hospitalization in the United States (U.S.) and across the world. In the U.S., there are over 1 million hospitalizations annually for AHF, costing on average almost $16,000 per admission.[1] Among those older than 65 years, AHF is the most common reason for emergency hospital admission and carries an estimated in-hospital mortality of 4% to 12% for those with acute on chronic heart failure (HF) and up to 60% for those presenting with cardiogenic shock.[2] Moreover, individuals who survive an AHF hospitalization remain at elevated risk for poor post-discharge outcomes including readmission and mortality. In recent years, many advances in the care of patients with AHF have occurred, and this subtype of HF remains an active area of investigation. In this article, we summarize contemporary data on the epidemiology, presentation, evaluation, and management of patients with AHF across phases of care, from the emergency room to the intensive care unit (ICU).

### DEFINITIONS AND CLASSIFICATIONS OF ACUTE HEART FAILURE

Definitions used in registries of AHF often include both acute *de novo* HF and acute decompensated HF. Acute *de novo* HF represents the first episode of cardiac decompensation in patients without a previously known history of HF, while acute decompensation occurs in patients with known chronic HF.[3] Variation exists across registries and guidelines, but most AHF definitions include (1) new or worsening symptoms, (2) escalation of care to urgent or emergent medical centers, and (3) treatment with intravenous or invasive therapies.[4] Even among those who meet criteria for AHF, there is marked heterogeneity in presentation, etiology of AHF, and subsequent management, which is challenging to encapsulate in a single

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definition. Recent revisions to the 2021 European Society of Cardiology guidelines stratify patients with AHF into 4 distinct subtypes: acute decompensated HF, acute pulmonary edema, isolated right ventricular failure, and cardiogenic shock, with different management algorithms for each.[5] There is also some disagreement about the distinct nature of AHF, particularly in patients who are hospitalized with gradual worsening of chronic symptoms rather than an acute precipitant.[6] For this article, both acute *de novo* and acute decompensated HF are addressed, and diagnostic tools and management are stratified by phase of care.

## EPIDEMIOLOGY OF ACUTE HEART FAILURE

Large-scale registries like Acute Decompensated Heart Failure National Registry (ADHERE), Organized Program to initiate Life Saving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF), and Acute Heart Failure Global Registry of Standard Treatment (ALARM-HF) provide epidemiologic insight into AHF, although the majority of these registries are based in the U.S. or Europe.[7,8] Male sex and advanced age are risk factors for development of AHF. Acute decompensation in those with known chronic HF, make up 70% of all AHF presentations, while *de novo* presentation is less common. The most common comorbidities include hypertension, coronary artery disease, and diabetes mellitus.[7] Patients presenting with *de novo* episodes of AHF are on average younger with less comorbidity and have higher inpatient mortality compared to those with chronic decompensated HF.[3] In-hospital mortality ranges from 4% to 14%, with highest in-hospital mortality for those requiring intensive care.[3,9] Mortality after discharge for AHF remains high despite advancements in therapy, and in some registries is up to 30% at 1 year post-discharge.[10] Almost 40% of all deaths and re-hospitalizations in the year following discharge are due to non-cardiac causes, reflecting the significant comorbidity burden of many patients hospitalized with AHF.[11]

Acute HF is commonly precipitated by acute coronary syndrome and ischemia, particularly for patients with *de novo* HF. Other precipitants include uncontrolled hypertension, arrhythmias, pulmonary emboli, valvular dysfunction, or systemic infection. For those with known HF, nonadherence to medications is a frequent cause of acute decompensation. Uncontrolled endocrine disorders (eg, hyperthyroidism, adrenal crisis), surgeries, anemia, and changes in medications that increase sodium retention are other possible acute precipitants.[12] For some patients, a cause may never be clearly identified. An expanded discussion on the precipitants of AHF is beyond the scope of this article and has been summarized elsewhere.[13–15]

## PHASE OF CARE: EMERGENCY DEPARTMENT

### *Presentation*

There are over 1 million emergency department (ED) visits for AHF in the U.S. each year.[16] Most patients present with congestive symptoms, with dyspnea being the most common reason for emergency evaluation.[7,8] The nonspecific nature of presenting symptoms can make the timely diagnosis of AHF challenging. In a meta-analysis of index tests to diagnose AHF in the ED, the presence of an S3 on physical examination had the highest positive likelihood ratio (4.0, 2.7 to 5.9) among all history and physical exam elements evaluated.[17] As there is no single clinical history or physical exam finding that can reliably rule in or rule out AHF, further diagnostic testing is essential.

### *Diagnostics*

Initial imaging should include a chest x-ray, which may show pulmonary venous congestion, pleural effusions, interstitial edema, or cardiomegaly. However, up to 20% of patients with AHF have a normal chest x-ray, so lack of congestion on imaging is not sufficient to exclude an HF diagnosis.[18] Point-of-care ultrasonography is being increasingly used to evaluate cardiac function expediently at the bedside. Obtaining views and estimates of the left ventricular ejection fraction, the inferior vena cava collapsibility, and the pleural space for signs of interstitial edema by experienced users has a specificity of nearly 100% for the diagnosis of AHF.[19] If a patient has new onset HF with no known clinical history, a formal echocardiogram should be obtained as soon as possible. Laboratory testing should include a complete blood count, electrolytes, creatinine and blood urea nitrogen, glucose, and cardiac troponin. Blood levels of natriuretic peptides, either b-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP), are highly sensitive and helpful to rule out AHF as the cause of presenting symptoms. A BNP of less than 100 pg/mL or NT-proBNP less than 300 pg/mL effectively excludes HF.[20] These biomarkers increase in response to ventricular dilatation and increased pressure, and the magnitude of elevation is correlated with illness severity and risk for mortality.[20,21] Of note, natriuretic peptide abnormalities should be interpreted with caution in patients with obesity or renal dysfunction, as obesity may falsely lower the value and renal dysfunction may falsely elevate it.[22,23] Sepsis, pulmonary hypertension, arrhythmia, and age also affect baseline natriuretic

peptide levels. In patients with chronic HF, change from individual baseline is more accurate for identifying acute decompensation than interpreting the absolute value, which may always be elevated above normal range.[20] It is also important to identify emergent causes of AHF for rapid intervention, for example, acute coronary syndromes, pulmonary embolism, and acute lung pathologies.

### *Management*

Assessment of respiratory status and risk of respiratory failure or hemodynamic compromise is essential immediately upon arrival to the emergency room. In AHF-related respiratory distress, noninvasive ventilation has been shown to reduce mortality and the need for intubation.[24] Intravenous loop diuretics should also be administered without delay, as early treatment is associated with reduced in-hospital mortality.[25] Intravenous vasodilators like nitroglycerin may also provide symptomatic relief, although they are contraindicated in patients with hypotension and concern for impending shock.[26]

### *Disposition*

Over 80% of patients presenting to the emergency room for AHF are admitted to the hospital, with the majority receiving care on inpatient units and 5% to 10% going directly to intensive care.[16] Patients with respiratory compromise or those who require noninvasive ventilation or endotracheal intubation in the ED should receive further care in the ICU. Hemodynamic instability measured by heart rate less than 40 or greater than 130 beats per minute or systolic blood pressure less than 90 or requiring intravenous inotropic or vasopressor support, is also an indication for transfer to a higher level of care.[27] The majority of patients without these signs can be safely managed on the inpatient floors.

Identifying lower risk patients with AHF who can be discharged home safely is challenging, and various risk stratification tools have been developed to guide disposition decisions in the ED. The Ottawa Heart Failure Risk Scale (OHFRS), Emergency Heart Failure Mortality Risk Group (EHMRG), Multiple Estimation of Risk Based on the Emergency Department Spanish Score in Patients with AHF (MEESSI-AHF), and St. Thomas Risk Assessment Tool in Falling elderly inpatients (STRATIFY) tools have been prospectively derived from patients in the ED with AHF to predict major adverse events at 30 days post-discharge (**Table 1**).[28] Most of these tools rely on readily available clinical variables obtained in the initial evaluation of AHF, but implementation and evaluation of subsequent patient-centered outcomes has been challenging.[29] Even in symptomatically improved patients, direct discharge from the emergency room to home is difficult to coordinate. High comorbidity burden, complex post-discharge follow-up needs, and elevated risk for higher post-discharge event rates and readmissions with direct discharge from the ED are contributing factors.[30] Patients may be admitted to observation units from the emergency room; however, studies comparing patients in observation have shown higher rates of cardiac and all-cause readmissions compared to those with inpatient stays, suggesting that the current admissions system still does not appropriately risk-stratify patients appropriate for observation status.[31] Further studies on risk stratification from the ED and randomized trials of these scoring systems are needed to improve patient outcomes and health system efficiency and resource utilization.

## PHASE OF CARE: INPATIENT FLOORS

### *Diagnostics*

Evaluation for the etiology of AHF and possible exacerbating factors should continue on the inpatient floor. This includes telemetry and blood pressure monitoring and evaluation for underlying infection. Signs and symptoms of congestion should be assessed daily. Screening for sleep apnea through careful history should also be performed on admission. Nutritional status and frailty should be assessed and multidisciplinary teams, including dieticians, physical therapy, and occupational therapy should be involved in care.[32]

For patients with newly diagnosed AHF, transthoracic echocardiography should be performed during the admission. In those with known chronic HF, echocardiography is indicated if there is a suspected significant change in cardiac function based on presentation.[32] Based on the history obtained from the patient and results of initial evaluation, catheterization, advanced imaging, or other laboratory tests may be indicated as well.[33]

### *Management*

Loop diuretics are the mainstay for decongestion, although direct evidence supporting their use in comparison to other diuretics and specific dosing regimens in AHF is lacking.[34] If decongestion remains challenging, the diuretic dose can be increased, or additional medications like thiazide diuretics, metolazone, or acetazolamide can be added for benefit. In the Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial, acetazolamide in combination with loop diuretics led to more successful decongestion and natriuresis in patients admitted to the hospital with AHF when compared with loop diuretic alone,

**Table 1**
**Selected risk stratification tools in acute heart failure**

| Location | Risk Tool | Year | Predicted Outcome | Variables and Performance |
|---|---|---|---|---|
| Emergency Department | Multiple Estimation of Risk Based on the Emergency Department Spanish Score in Patients with AHF (MEESSI-AHF)[84] | 2019 | 30-d mortality | Incorporates 13 variables, including Barthel Index at ED admission, vital signs and ED labs, NYHA class, low output symptoms, ACS symptoms, and hypertrophy on ECG<br>c-statistic = 0.83 |
| | Emergency Heart Failure Mortality Risk Group (EHMRG)[85] | 2019, 2012 | 7- and 30-d mortality | Incorporates 10 variables to identify patients at low risk for mortality, including ED vitals and labs, history of active cancer, transport by emergency medical services, and metolazone at home<br>c-statistic = 0.80 |
| | Ottawa Heart Failure Risk Scale[86] | 2017, 2013 | 30-d SAE (death, admission to monitored unit, intubation, ventilation, myocardial infarction, or relapse resulting in hospital admission within 14 d | Incorporates 10 variables including history of stroke/TIA, prior intubation, ED vital signs and labs, and ischemic ECG changes<br>c-statistic = 0.78 |
| | STRATIFY[87] | 2015 | 5- and 30-d hierarchical SAE (acute coronary syndrome, coronary revascularization, emergent dialysis, intubation, mechanical cardiac support, cardiopulmonary resuscitation, and death) | Age, BMI, ED vital signs and laboratory values, dialysis, supplemental oxygen use, and QRS duration<br>c-statistic = 0.68 |
| | Kaiser Permanente Northern California (KPNC) ED AHF[88] | 2020 | 30-d SAE (acute coronary syndrome, coronary revascularization, emergent dialysis, intubation, mechanical cardiac support, cardiopulmonary resuscitation, and death) | Using STRATIFY as its base, this risk tool added 58 additional variables, including medical comorbidities, medications, health care utilization and additional ED vital signs, among others<br>c-statistic = 0.85 |

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| Inpatient | ADHERE[55] | 2005 | In-hospital mortality | Simple model incorporating BUN, creatinine, systolic blood pressure<br>c-statistic = 0.75 |
| | OPTIMIZE-HF[9] | 2008 | In-hospital mortality | Age, race, admission labs, history of liver disease, stroke, peripheral vascular disease, or chronic obstructive lung disease, previous HF hospitalization, systolic blood pressure<br>c-statistic = 0.72 |
| | ELAN-HF[56] | 2014 | 180-d mortality post-discharge | NT-proBNP at discharge and reduction in admission, age, peripheral edema, serum sodium and urea, systolic blood pressure, NYHA class on admission<br>c-statistic = 0.75 |
| | ADHF/NT-proBNP risk score[57] | 2013 | 6-mo mortality post-discharge | NT-proBNP, history of chronic obstructive pulmonary disease, serum sodium, hemoglobin, and glomerular filtration rate, left ventricular ejection fraction and tricuspid regurgitation, systolic blood pressure<br>C-statistic = 0.77 |
| Intensive care | Society for Cardiovascular Angiography and Interventions (SCAI) stages[63] | 2019 | In-hospital mortality from cardiogenic shock | Stages patients into 5 categories (Stage A through E) based on physical exam findings, creatinine, lactate, liver function tests, BNP, and hemodynamic data, as well as response to intensive treatment.<br>Increasing stage is associated with higher in-hospital mortality |

*Abbreviations:* ACS, acute coronary syndrome; BMI, body mass index; BUN, blood urea nitrogen; ECG, electrocardiogram; ED, emergency department; HF, heart failure; NYHA, New York Heart Association; SAE, serious adverse event; TIA, transient ischemic attack.

along with shorter hospitalizations and reduced signs of volume overload on discharge.[35] Decongestion should continue until euvolemia is reached.[36] Physical markers of euvolemia include jugular venous pressure (JVP) reduction to less than 8 cm, resolved dyspnea at rest, and resolution of any orthopnea or edema noted on admission. Incomplete resolution of signs and symptoms of volume overload at the time of discharge is associated with higher rates of re-hospitalization and death.[37] Monitoring of electrolytes and kidney function should continue at least daily during diuresis. Transient rise in serum creatinine during diuresis is expected and does not represent worsening renal function or renal injury.[38] For most patients with AHF, pulmonary artery catheterization for clinical assessment of volume status is not indicated.[12] The use of invasive hemodynamics has not been shown to affect overall mortality and hospitalization rates for patients not at risk for the development of cardiogenic shock.[39] For some patients, invasive hemodynamic monitoring may be useful for guide treatment; clinical trials (eg, NCT05485376) are currently ongoing for further investigation from which patients may benefit.[40]

Once euvolemia is reached, patients are typically transitioned to oral diuretic doses for maintenance and monitored for at least 24 hours on oral medications alone. However, recent evidence suggests that this practice does not benefit patients and may only increase length of hospital stay, as no association between in-hospital observation on oral diuretics and accurate outpatient diuretic dosing or reduction in readmissions was observed in a multicenter cohort.[41]

For patients with AHF with reduced ejection fraction, hospitalization is an opportunity to titrate and optimize medication regimens. Patients already on guideline-directed medical therapy (GDMT) prior to admission should continue their home medications unless there is a clear contraindication, as there is mortality benefit to continuing all forms of GDMT during hospitalization (**Tables 2** and **3**). Beta blockers should only be held or dose-reduced in patients with low cardiac output and features concerning for cardiogenic shock. In OPTIMIZE-HF, discontinuation of beta blockers in the inpatient setting was associated with higher risk of mortality.[42] Discontinuation of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) among hospitalized patients in the Get With The Guidelines-Heart Failure (GWTG-HF) registry was also associated with higher mortality and readmission rates.[43] Mineralocorticoid receptor antagonists like spironolactone should also be continued, as continuation was shown to decrease rates of rehospitalization and 30-day mortality in the Comparison of Outcomes and Access to Care (COACH) study.[44] These therapies should be continued despite mild fluctuations in creatinine with diuresis, which are expected and do not represent a true renal tubular injury but likely represent changes in filtration as a result of diuresis and medication adjustments.[45]

Patients with newly diagnosed HF with reduced ejection fraction should be initiated on GDMT during the index admission (see **Tables 2** and **3**). Several trials studying initiation of beta blockers, ACEi/ARB/angiotensin receptor/neprilysin inhibitor (ARNI), mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 (SGLT2)-inhibitors have shown improvements in mortality and decreased readmission rates with in-hospital prescription and uptitration prior to discharge.[43,46,47]

Iron deficiency is common among patients with AHF and associated with worse outcomes.[48,49] In the AFFIRM-HF trial, patients hospitalized with AHF with reduced ejection fraction and transferrin saturation less than 20% were treated with intravenous repletion with ferric carboxymaltose. This led to reduced cardiovascular deaths and recurrent hospitalizations for HF.[50] Iron studies should be checked on all patients hospitalized with AHF and repleted if indicated, regardless of hemoglobin level.

For patients with AHF with preserved ejection fraction, evidence-based therapies are more limited. Diuresis should be similarly used to improve symptoms and reach euvolemia. As poorly controlled hypertension is often a precipitant of this type of HF, control of blood pressure and medication titration while inpatient may be beneficial.[51] SGLT2 inhibitors have also shown benefit in this population, demonstrating a significant reduction in HF hospitalizations and improvement in quality of life in the EMPEROR-Preserved Trial.[52] Safety and tolerability of in-hospital SGLT2 inhibitor initiation was shown in the EMPULSE trial, and patients accrued significant clinical benefit even up to 90 days after discharge.[53]

### *Disposition*

Several prognostic models have been developed to predict in-hospital and post-hospitalization outcomes in patients with AHF, although clinical application of these models remains difficult (see **Table 1**). Most of these risk scores use various combinations of presenting vital signs, comorbidities, and objective data including measures of renal function and electrolytes as predictive variables, but applicability at an individual patient-level is difficult to ascertain, and there is marked variability

**Table 2**
**Selected observational studies of contemporary guideline-directed medical therapy in acute heart failure**

| Medication Class | Trial/Study (Author, Year) | Source of Data | Number of Patients | Follow-up Duration | Endpoints of Interest | Results |
|---|---|---|---|---|---|---|
| Beta-blocker (BB) | OPTIMIZE-HF (Fonarow et al., 2008)[42] | 91 hospitals participating in the OPTIMIZE-HF hospital registry | 2373 patients eligible for BB at discharge<br>1350 (56.9%) on BB before admission and continued on<br>632 (26.6%) BB newly started<br>79 (3.3%) BB withdrawn<br>303 (12.8%) BB eligible but not treated | 60- to 90-d post-discharge | Post-discharge death and death/rehospitalization | BB continuation associated with lower post-discharge death (HR: 0.60; 95% CI: 0.37–0.99, $P = .044$) and death/rehospitalization (OR 0.69; 95% CI: 0.52–0.92, $P = .012$) risk compared with no BB<br>BB withdrawal associated with higher mortality compared with BB continuation (HR: 2.3; 95% CI: 1.2–4.6, $P = .013$) |
| Mineralocorticoid receptor antagonists (MRA) | ALARM-HF (Bistola V et al., 2018)[89] | Acute Heart Failure Global Registry of Standard Treatment study cohort | 4953 patients in original study cohort<br>1439 MRA-treated and 3514 untreated<br>Propensity score with 1:1 matching yielded N = 1003 in each group | Up to 30 d from discharge | All-cause death during hospitalization | 4.2% vs 10.8% in MRA treated vs untreated patients<br>Treatment with MRAs was associated with a reduction of in-hospital mortality [HR 0.372 (95% CI, 0.261–0.532, $P < .001$) |
| | Yaku et al,[90] 2019 | Kyoto Congestive Heart Failure registry | 3717 patients hospitalized for ADHF<br>1678 (45.1%) received MRA at discharge, 2039 (54.9%) did not | Mean 470 d (357–649 d) | Composite of all-death or heart failure hospitalization after discharge | MRA use was associated with lower incidence of HF hospitalization (18.7% vs 24.8%, HR 0.70, 95% CI 0.60–0.86; $P < .001$) |

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**Table 2**
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| Medication Class | Trial/Study (Author, Year) | Source of Data | Number of Patients | Follow-up Duration | Endpoints of Interest | Results |
|---|---|---|---|---|---|---|
| | | | Matched cohort<br>N = 1034 | | | No difference in mortality between the 2 groups (15.6% vs 15.8%; HR 0.98, 95% CI 0.82–1.18, $P = .85$) or in all-cause hospitalization (35.3% vs 38.2%; HR, 0.88; 95% CI, 0.77–1.01; $P = 0.07$) |
| Angiotensin neprilysin inhibitor (ARNI) | Carnicelli et al,[91] 2021 | Get With the Guidelines-Heart Failure registry linked with Medicare claims | 897 patients discharged on sacubitril/valsartan<br>295 (32.9%) PDC > 80%<br>602 (67.1%) PDC < 80% | Adherence 90 d post-discharge<br>Follow up at 1 y | Adherence, assessed using medication fills to calculate proportion of days covered (PDC)<br>Risk of readmission and death within 1 y | Adherence to sacubitril-valsartan was associated with lower risk of all cause rehospitalization (HR: 0.66 [95% CI: 0.48–0.89) and death (HR: 0.42 [95% CI: 0.22–0.79]) at 90 d and at 1 y (HR: 0.69 [95% CI: 0.56–0.86] and HR: 0.53 [95% CI: 0.38–0.74], respectively) |

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| SGLT2 inhibitor | Martin et al,[92] 2021 | | 102 patients discharged for acute HF<br>45 (44.1%) prescribed canagliflozin<br>57 (55.9%) not prescribed any SGLT-2 inhibitor | 22 mo | Adverse clinical events (HF rehospitalization and cardiovascular death)<br>NT-proBNP changes | Canagliflozin use was associated with a lower risk of HF readmission at first year (22.2% vs 49.1%, HR: 0.45; 95% CI: 0.21–0.96; $P < .039$)<br>Composite outcome (hospitalization for HF, death from cardiovascular cause) was lower in the canagliflozin group vs control (37.8% vs 70.2%, HR: 0.51; 95% CI: 0.27–0.95; $P < .035$) |
| | Perez-Belmonte et al,[93] 2022 | Four hospitals in Malaga, Spain | 208 of 518 patients hospitalized with T2DM for AHF were > 80 year old<br>99 (47.6%) continued empagliflozin, 109 (52.4%) on basal bolus<br>79 propensity matched patients in each group | Discontinued due to loss of funding | Clinical efficacy (measured by visual analogue dyspnea score, NT-proBNP level, diuretic response, cumulative urine output)<br>Safety endpoints: adverse events, worsening HF, discontinuation of empagliflozin, length of stay, in-hospital deaths | Empagliflozin was associated with lower NT-proBNP levels ($1699 \pm 522$ vs $2303 \pm 598$ pg/mL, $P = .021$)<br>Empagliflozin led to a greater diuretic response (weight loss/40 mg furosemide) and cumulative urine output ($-0.14 \pm -0.06$ vs $-0.24 \pm -0.10$, $P = .044$; and $16{,}100 \pm 1510$ vs $13{,}900 \pm 1220$ mL, $P = .037$, respectively) |

*Abbreviations:* ADHF, acute decompensated heart failure; CI, confidence interval; HF, heart failure; HR, hazard ratio; OR, odds ratio; T2DM, type 2 diabetes mellitus.

**Table 3**
**Selected ongoing and completed randomized trials of contemporary guideline-directed medical therapy in acute heart failure**

| Medication Class | Trial/Study (Author, Year) | Source of Data | Patient Population | Number of Patients & Trial Arms | Primary Endpoint | Results |
|---|---|---|---|---|---|---|
| Beta-blocker (BB) | IMPACT-HF (Gattis et al,[94] 2004) | Multicenter (45) across U.S. | LVEF < 40% + hospitalized for HF | N = 185 pre-discharge carvedilol initiation<br>N = 178 physician discretion post-discharge initiation | Number of patients treated with any BB at 60 d after randomization | Patients randomized to carvedilol initiation predischarge arm were more likely to be treated with any BB at 60 d vs those randomized to the physician-discretion post-discharge BB initiation arm (91.2% vs 73.4%, $P < .0001$) |
| Mineralocorticoid receptor antagonists (MRA) | Ferreira et al,[95] 2013 | Prospective, experimental single-center, single-blinded | Hospitalization due to decompensated chronic heart failure | N = 100 patients enrolled<br>N = 50 patients in treatment group, 50 patients in placebo | Proportion of patients free of congestion at day 3 (defined as JVP < 8 cm, no orthopnea, no lower extremity edema) | Patients treated with spironolactone were more likely to be free of congestion at day 3: lack of edema (32% vs 66%, $P = .001$), no rales (24% vs 66%; $P < .001$), JVP < 8 cm (90% vs 100%; $P = .02$), and no orthopnea (76% vs 96%; $P = .004$) |

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| | ATHENA-HF (Butler et al,[96] 2017) | Double-blind randomized clinical trial in 22 US acute care hospitals | Hospitalized patients with AHF who previously receiving no or low dose spironolactone, NT-proBNP > 1000 pg/mL, BNP > 250 pg/mL | N = 360 patients enrolled<br>N = 182 (50.6%) patients randomized to receive spironolactone<br>N = 178 (49.4%) to usual care alone<br>N = 132 placebo, 46 low-dose spironolactone | Change in NT-proBNP levels from baseline to 96 h | There was no significant reduction in log NT-proBNP level between two groups: −0.55 [95% CI, −0.92 to −0.18] with high-dose spironolactone and −0.49 [95% CI, −0.98 to −0.14] with usual care, $P = .57$<br>No significant difference in 30-d all-cause mortality or heart failure hospitalization rate |
| | EARLIER (Asakur et al,[97] 2022) | Multicenter, randomized, double-blind across 27 Japanese institutions | Age > 20 year old, LVEF < 40% | N = 300 patients<br>N = 149 (49.7%) in eplerenone<br>N = 151 (50.3%) in placebo group | Composite cardiac death or first re-hospitalization due to cardiovascular disease within 6 mo | The study was inadequately powered to detect a significant association between initiation of eplerenone and rates of cardiac death or hospitalization (19.5% vs 17.2%, HR 1.09, 95% CI 0.642–1.855) |

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**Table 3**
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| Medication Class | Trial/Study (Author, Year) | Source of Data | Patient Population | Number of Patients & Trial Arms | Primary Endpoint | Results |
|---|---|---|---|---|---|---|
| Angiotensin neprilysin inhibitor (ARNI) | PIONEER-HF (Velazquez et al,[98] 2019) | Multicenter, randomized, double-blind trial across 129 sites in the United States | LVEF < 40%, or NT-proBNP > 1600 pg/mL, or BNP > 400 pg/mL, and received a diagnosis of ADHF | N = 881 patients randomized<br>N = 440 sacubitril-valsartan<br>N = 441 to receive enalapril | Time-averaged proportional change in NT-proBNP concentration through weeks 4 and 8 | Initiation of sacubitril-valsartan led to a greater reduction in NT-proBNP level (0.53 vs 0.75, percent change, −46.7% vs −25.3%; ratio of change with sacubitril-valsartan vs enalapril, 0.71; 95% CI, 0.63–0.81; $P < .001$) |
| | TRANSITION (Wachter et al,[99] 2019) | Multicenter, randomized, open-label study | Hospitalized for an episode of ADHF, blood pressure > 100 mm Hg, LVEF < 40% | N = 1002 randomized<br>N = 500 patients randomized to pre-discharge initiation<br>N = 502 patients randomized to post-discharge initiation | Proportion of patients attaining 97/103 twice daily target dose after 10 wk | Comparable proportions of patients in each arm attained target dose after 10 wk ([45.4% vs 50.7%; RR 0.90; 95% CI 0.79–1.02], suggesting either in-hospital or shortly after discharge initiation is feasible |
| | PARAGLIDE-HF (Mentz et al,[100] 2023) | Double-blind, randomized control trial | LVEF > 40%, elevated NT-proBNP or BNP level | N = 466 patients<br>N = 233 sacubitril/valsartan<br>N = 233 valsartan | Time-averaged proportional change in NT-proBNP from baseline through weeks 4 and 8 | Sacubitril/valsartan was associated with significant NT-proBNP reduction (ratio of change: 0.85; 95% CI: 0.73–0.999; $P = .049$). |
| | PREMIER[101] | Multicenter, open-label, blinded randomized control study | NYHA class II-IV, hospitalized for ADHF, currently taking an ACE-inhibitor or ARB, NT-proBNP > 1200 pg/mL, BNP > 300 pg/mL | N = 400 patients | Change in NT-proBNP concentrations from baseline to 8 wk | Estimated study completion date: March 2025 |

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|---|---|---|---|---|---|---|
| SGLT2 inhibitor | EMPA RESPONSE-AHF (Damman et al,[102] 2020) | Randomized, double blind, multicenter pilot study | Patients with and without T2DM, admitted for ADHF | N = 80, randomized 1:1 to receive empagliflozin 10 mg vs placebo | Change in visual analogue scale dyspnea score, diuretic response, change in NT-proBNP, and length of stay | Empagliflozin was associated with recued combined endpoint of in-hospital worsening of HF, rehospitalization, or death at 60 d (4 vs 13; $P = .014$), although no difference was observed in visual analogue scale dyspnea score, diuretic response, length of stay, or change in NT-proBNP level |
| | SOLOIST-WHF (Bhatt et al,[47] 2021) | Multicenter, double-blind trial | Patients with T2DM recently hospitalized for worsening HF | N = 1222 randomized<br>N = 608 to sotagliflozin<br>N = 614 to placebo | Total number of deaths from cardiovascular events, hospitalizations, and urgent visits for HF | Sotagliflozin associated with significantly fewer primary endpoint events (245 vs 355, 51.0 vs 76.3; HR, 0.67; 95% CI, 0.52–0.85; $P < .001$) |
| | Tamaki et al,[103] 2021 | Prospective, single-center, randomized, open label | Patients with T2DM admitted for ADHF | N = 59 consecutive patients<br>N = 30 to empagliflozin<br>N = 29 to conventional glucose lowering therapy | Decongestion based on NT-proBNP levels | Empagliflozin was associated with significantly lower NT-proBNP level at 7 d ($P = .040$) |
| | EMPULSE (Voors et al,[53] 2022) | Multicenter, randomized, double blind trial across 118 sites in 15 countries | Hospitalized for AHF with 2 of the following: congestion on chest x-ray, rales on auscultation, elevated JVP, lower extremity edema | N = 530 randomized<br>N = 265 empagliflozin<br>N = 265 placebo | Hierarchical composite of death from any cause, number of HF events and time to first HF event, or a 5 point or greater difference in change from baseline in the | Empagliflozin was associated with clinical benefit over placebo (stratified win ratio 1.36, 95% CI 1.09–1.68, $P = .0054$) |

(*continued on next page*)

**Table 3**
**(*continued*)**

| Medication Class | Trial/Study (Author, Year) | Source of Data | Patient Population | Number of Patients & Trial Arms | Primary Endpoint | Results |
|---|---|---|---|---|---|---|
| | | | | | Kansas City Cardiomyopathy Questionnaire Total Symptoms Score, assessed using a win ratio | |
| | DELIVER (Solomon et al,[104] 2022) | Multicenter, double-blind randomized control | LVEF < 40%, evidence of structural heart disease, elevated BNP | N = 6263 patients randomized<br>N = 3131 dapagliflozin<br>N = 3132 placebo | Composite of worsening heart failure or cardiovascular death | The primary outcome occurred less frequently in the dapagliflozin group (512 (16.4%) vs 610 (19.5%), HR, 0.82; 95% CI, 0.73–0.92; $P < .001$) |
| | Charaya et al,[105] 2022 | Single-center, controlled, randomized study | AHF hospitalization with planned administration of loop diuretics, LVEF < 50% | N = 102 randomized<br>N = 50 dapagliflozin<br>N = 52 standard therapy | Renal function deterioration | Although GFR decreased in 48 h in the dapagliflozin ($-4.2$ ($-11.03$; 2.28) mL/min vs 0.3 ($-6$; 6) mL/min; $P = .04$), renal function did not differ on discharge ($54.71 \pm 19.18$ mL/min and $58.92 \pm 24.65$ mL/min; $P = .36$) |
| | EMPAG-HF (Schulze et al,[106] 2022) | Single center, prospective, double-blind, placebo-controlled randomized study | BNP > 100 pg/mL, NT-proBNP > 300 pg/mL | N = 60 randomized | Cumulative urine output over 5 d | Use of empagliflozin increased urine output by 25% over 5 d (10.8 vs 8.7 L, 2.2 L difference, [95% CI, 8.4–3.6]; $P = .003$) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Thiele et al,[107] 2022 | Prospective, placebo-controlled, double-blind exploratory study | NT-proBNP > 1000 pg/mL | N = 19 study participants, received 10 mg or placebo | Cardiac output as determined by ClearSight System | Empagliflozin did not affect cardiac index or systemic vascular resistance, although reduced parameters of AKI (placebo: 1.1 ± 1.1 (ng/mL)2/1000; empagliflozin: 0.3 ± 0.2 (ng/mL)2/1000; $P = .02$) |
| | DICTATE-AHF[108,109] | Prospective, multicenter, open-label randomized trial | Patients with T2DM hospitalized with AHF, GFR > 30 | N = 240 patients planned for enrollment, randomized 1:1 to dapagliflozin 10 mg or usual care | Diuretic response, defined as cumulative change in weight per cumulative loop diuretic dose (40 mg IV furosemide equivalent) | Estimated study report date: August 2023 |
| | DAPA ACT HF-TIMI 68[110] | Multicenter, randomized, double-blind placebo controlled trial | For LVEF < 40%: NT-proBNP > 1600 pg/mL, BNP > 400 pg/mL<br>For LVEF > 40%: NT-proBNP > 1200 pg/mL, BNP > 300 pg/mL | N = 2400 participants | CV death or worsening heart failure | Estimated study completion date: March 2024 |
| Ferric carboxymaltose | AFFIRM-AHF (Ponikowski et al,[50] 2020) | Multicenter, double -blind, randomized trial at 121 sites in Europe, South America, and Singapore | Hospitalized for acute heart failure with iron deficiency (ferritin < 100, or 100–299 with transferrin saturation < 20%), LVEF < 50% | N = 1132 randomly assigned<br>N = 1108 with at least 1 post-randomization value (558 in ferric carboxymaltose vs 550 placebo) | Composite of total hospitalization for HF and CV death 52 wk after randomization | Treatment with ferric carboxymaltose was associated with lower rates of HF hospitalization (217 vs 294, RR 0.74; 95% CI 0.58–0.94, $P = .013$), although no effect on CV mortality (77 (14%) vs 78 (14%), HR 0.96, 95% CI 0.70–1.32, $P = .81$) |

*Abbreviations:* ACE, angiotensin-converting enzyme; ADHF, acute decompensated heart failure; AHF, acute heart failure; AKI, acute kidney injury; ARB, angiotensin receptor blockers; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; NYHA, new york heart association; RR, risk ratio.

among prognostic models depending on the variables selected.[54] Tools like the ADHERE score and OPTIMIZE-AF registry score have good performance predicting in-hospital mortality for admitted patients.[9,55] For outcomes post-discharge, the ELAN-HF score and ADHF/NT-proBNP risk score are effective for predicting 180 day and 1-year mortality post-discharge, respectively.[56,57]

Patients who achieve decongestion and have undergone therapeutic optimization can be discharged with clear plans for rescue dosing of diuretics in case of weight gain at home, as well as with instructions for fluid restriction and standing electrolyte supplementation if needed.[32] If medication or dietary nonadherence were suspected as triggers of decompensation, patient concerns and barriers to adherence should be fully addressed at the time of discharge.

Up to 25% of patients will be readmitted after 30 days after a hospitalization for AHF.[58] The transition between inpatient and outpatient care is a particularly vulnerable time, and efforts should be made during hospitalization to coordinate care and ensure close follow-up with a specialized team. A post-discharge clinic visit should occur within 1 week of hospitalization and should focus on review of symptom trajectory, medication reconciliation, management of comorbidities, safety, laboratory testing, patient education, and advance care planning. Titration of GDMT, assessment of volume status, and adjustments in diuretic dosing to maintain euvolemia should be focuses of initial outpatient follow-up.[59] For patients with *de novo* AHF, a repeat assessment of left ventricular systolic function should occur within 3 months of hospital discharge for evaluation of primary pretention defibrillator implantation.[12] A multidisciplinary approach, with case management involvement for high-risk patients, visits to the home, and outreach via phone or other mechanisms when possible is helpful to prevent readmissions and reduce mortality.[60] Cardiac rehabilitation referrals should be in place for all patients discharged from the hospital, as supported by the REHAB-HF trial which showed that cardiac rehabilitation participation led to improvements in physical functioning without causing harm, even in the elderly or frail.[61]

Inability to achieve decongestion despite escalating diuretic doses is 1 indication for transfer to a higher level of care. These patients may require transfer to the ICU for invasive monitoring and consideration of mechanical support in case of worsening cardiogenic shock. Invasive hemodynamic monitoring with pulmonary artery catheterization may provide helpful guidance for effective diuresis and augmentation from intravenous vasodilators or inotropic therapy.

## INTENSIVE CARE UNIT

### *Presentation*

An estimated 20% of patients hospitalized with HF require admission to the ICU at some point during their stay.[62] Patients with AHF requiring ICU support often present in cardiogenic shock, characterized by hypotension (systolic blood pressure < 90 mm Hg or mean arterial blood pressure <60 mm Hg) with other signs of hypoperfusion, including cold extremities, low urine output, altered mental status, or elevated lactate.[63] Mortality rates are high for this population, with some studies estimating short-term mortality of almost 40%.[64] Physical examination is the first important step in diagnosing AHF and cardiogenic shock. Many patients present with a “cold and wet” hemodynamic profile, although some with decompensated chronic HF may present without signs of overt congestion.[62]

### *Diagnostics*

In addition to the previously discussed diagnostic tools, pulmonary artery catheterization for hemodynamic monitoring is associated with lower mortality in patients with cardiogenic shock.[65] The 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America HF guidelines recommend obtaining invasive hemodynamic data when escalation to mechanical support is being considered or when there is diagnostic uncertainty regarding the etiology of shock in patients with AHF.[12]

### *Management*

Careful monitoring of respiratory status is essential, as elevated ventricular filling pressures and subsequent cardiogenic pulmonary edema can cause significant hypoxemia and hypercarbia. Noninvasive positive pressure ventilation (NIPPV) helps to reduce work of breathing, increase lung compliance, and recruit alveoli.[66] Studies have shown reduction in both intubation rates and in-hospital mortality with use of NIPPV.[67] If hypoxemia and hypercarbia persists with NIPPV, endotracheal intubation can decrease left ventricular afterload and improve both oxygenation and cardiac index.[66] Caution is warranted, as anesthesia induction and continued sedation may cause more harm in those with significant right ventricular dysfunction.

In patients with cardiogenic shock, vasopressors and inotropes should be considered to address hemodynamic instability and rapidly improve organ perfusion. Dobutamine and milrinone are common first choice agents in cardiogenic shock because

of both inotropic and vasodilatory properties.[62] Studies have shown no difference in in-hospital mortality or adverse effects between the 2 agents.[68] Norepinephrine is the first-line vasopressor of choice in HF and increases both systemic vascular resistance and cardiac output. Epinephrine is associated with increased incidence of arrhythmia and refractory shock compared to norepinephrine and is less frequently used.[69,70] Dopamine is similarly associated with increased risk of death in patients with cardiogenic shock.[71] Vasopressin is often used in addition to norepinephrine and is particularly beneficial in right ventricular failure due to increase in pulmonary vasodilation.[62] While vasopressors can help sustain mean arterial pressure, their use increases left ventricular afterload and can cause myocardial ischemia.[62]

Mechanical circulatory support (MCS) provides increased circulatory support beyond what can be achieved through inotropic infusions. Temporary forms of MCS help to stabilize patients in the acute setting and allow time for either recovery or multidisciplinary discussions about transitions to durable MCS or cardiac transplantation. While there is a paucity of data directly comparing MCS options, and most studies have been performed in patients with acute myocardial infarction and subsequent shock, MCS use has increased exponentially over the last few decades even in patients with AHF unrelated to myocardial infarction.[72]

Current U.S. society guidelines list temporary MCS as a class 2a recommendation for the management of patients with cardiogenic shock.[12] The intra-aortic balloon counter-pulsation pump is the most frequently used device as first-line temporary circulatory support for patients in AHF.[73] The Intra-aortic Balloon Counterpulsation in Cardiogenic Shock II trial showed that use of intra-aortic balloon pump (IABP) did not significantly reduce 30- or 1-year mortality for patients with cardiogenic shock from acute myocardial infarction (AMI-CS).[74] However, in patients with cardiogenic shock from HF (HF-CS), IABP use is associated with improved outcomes when used as a bridge to durable MCS or cardiac transplantation.[75] This patient population is currently being enrolled in the Altshock-2 trial, a prospective, randomized, multicenter, open-label study in which patients with acute HF-CS will be randomized to early IABP implantation or to vasoactive treatments with a primary end point of 60 days patients' survival or successful bridge to heart replacement therapy.[76] The Impella is a continuous-flow axial pump placed across the aortic valve into the left ventricle, which produces flow from the left ventricle to the ascending aorta at set rates, reducing myocardial oxygen demand and ventricular wall stress. Retrospective studies have not shown a mortality benefit of the Impella compared to the IABP in patients with AMI-CS,[77] and there are a number of ongoing studies and registries of Impella use in CS. Venoarterial extracorporeal membrane oxygenation is an additional temporary MCS strategy and has been associated with worse survival compared with IABP and other temporary MCS platforms in patients being bridged to durable MCS.[78]

A high proportion of patients who are bridged to durable left ventricular assist device reach discharge, and this may serve as destination therapy for some.[79] Patients with refractory HF may also be considered for heart transplantation. Those who do not experience recovery and are not deemed to benefit from advanced therapies should be palliated.

### *Outcomes and Disposition*

Patients who require intensive care at any point during their hospitalization have higher mortality at 30-days and 1 year after hospitalization, as well as higher rates of readmission.[80] Elevated biventricular filling pressures, low systemic blood pressure, and elevated markers of end-organ perfusion on admission to intensive care are associated with higher mortality.[73] The Society for Cardiovascular Angiography and Interventions (SCAI) staging system use some of these biochemical and hemodynamic findings to risk stratify patients with cardiogenic shock and increasing shock severity stage is associated with increased in-hospital mortality for patients in AHF.[81]

Those who improve in intensive care will transition to inpatient floors, where their medications can be adjusted and optimized in preparation for discharge. However, there are a significant proportion of patients who do not survive to discharge from the ICU. For these patients, palliative care is an integral part of their care. Early integration of palliative care can ensure patients' wishes are respected in the setting of critical illness and are an essential part of compassionate, patient-centered care at the end of life.[82] Patients who participate in interdisciplinary palliative care intervention have improvements in quality of life, anxiety, depression, and spiritual well-being.[83]

## SUMMARY

AHF remains a significant public health challenge, and as the prevalence of HF continues to rise, an increasing number of individuals will be at elevated risk for hospital readmission and mortality. There is a paucity of high-quality evidence to guide the care of patients with AHF, and further studies focused

on optimal timing of deployment of stabilizing therapies are urgently needed. Nevertheless, the AHF period is an opportune time to optimize evidence-based medical therapy for HF, and linkage to outpatient care is essential to improve outcomes.

## CLINICS CARE POINTS

- Among those older than 65 years, AHF is the most common reason for emergency hospital admission.
- Acute decompensated HF in those with known chronic HF make up 70% of all AHF presentations.
- For patients with AHF with reduced ejection fraction, hospitalization is a golden opportunity to optimize guideline directed medical therapy.
- Discontinuation of guideline directed medical therapy for HFwith reduced ejection fraction during hospitalization for AHF has been associated with higher risk of mortality and higher readmission rates.

## DISCLOSURE

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